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Transoesophageal Echocardiography in Patients without Arterial and Major Cardiac Sources of Embolism: Difference between Stroke Subtypes

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Key Words
Cardioembolic stroke · Transoesophageal echocardiography · Patent foramen ovale · Atrial septal aneurysm

Abstract
We studied the records of 175 consecutive patients referred to our neurologic ward between January 1994 and February 2000 with a diagnosis of ischaemic cerebrovascular disease (ICVD) (stroke or transient ischaemic attack – TIA) who underwent transoesophageal echocardiography (TEE). We excluded patients with large vessel disease, high-risk embolic cardiopathies and other rare causes of stroke. According to clinical and neuroimaging findings, patients were divided into two groups. The lacunar (LAC) group (69/175 (39.4%)) and the nonlacunar (N-LAC) one (106/175 (60.6%)). The control population consisted of 78 consecutive patients, referred to the echocardiography laboratory for TEE without history of ICVD and known heart disorders. Patent foramen ovale (PFO) frequency was significantly higher in case patients than in control subjects (55/175 (31.4%) vs. 13/78 (16.6%); p = 0.02). Among case patients, PFO was more prevalent in the N-LAC group than in the LAC one (43/106 (40.6%) vs. 12/69 (17.4%); p = 0.0005). A large degree of shunt occurred in 53.5% of N-LAC patients and in 16.7% of LAC ones (p = 0.04). Atrial septal aneurysm (ASA) was detected in 12% of case patients and 1.3% of control subjects (p = 0.003) and was more frequent in the N-LAC group than in the LAC one (16 vs. 5.8%; p = 0.05). Mitral prolapse (MP) was present in 6/175 (3.4%) ICVD patients (vs. 1/78 among controls) in most cases associated with myxomatous valve redundancy. Aortic arch atheromas (AA) were detected in 12% of ICVD patients and in 10.2% of controls. The frequency was 9.4% in N-LAC and 15.9 in LAC. No complicated AA (plaque thickness >4 mm, ulcerated atheroma, superimposed thrombus) were detected. After multivariate analysis, PFO (OR = 3.8; 95% CI = 2.7–7.9) and ASA (OR = 8.01; 95% CI = 3.0–16.1) appeared to be independent predictors of ICVD. PFO (OR = 2.24; 95% CI = 1.24–4.92) was also independently associated with N-LAC stroke subtype and its importance was even higher in younger patients. Our study provides further evidence that TEE is a helpful diagnostic tool in stroke patients without arterial and major cardiac sources of embolism. However, its utility differs according to type and localization of the ischaemic lesion being more relevant in patient with N-LAC infarctions.

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Introduction

Transoesophageal echocardiography (TEE) represents the method of choice for the detection of left atrium and appendage thrombi [1] and is essential in the assessment of aortic arch atheromas (AA) [2] and of several cardiopathies often considered minor cardiac sources of embolism (CSE) such as atrial septal aneurysm (ASA), patent foramen ovale (PFO), mitral valve prolapse (MP), myxomatous mitral degeneration (MMD), mitral annulus calcification, aortic calcific stenosis, mitral strands and spontaneous echocontrast [3–13]. Although several classifications have been proposed [10–13], at the moment a widely accepted stroke risk stratification for minor CSE does not exist. Whereas the so-called 'high-risk' cardiac embolic sources are considered determined causes of ischaemic cerebrovascular disease (ICVD), minor CSE are often defined as 'low-risk' or uncertain embolic sources [13]. In ICVD it may be difficult to sustain a defined role for minor CSE (in particular PFO) because of their high prevalence in the general population [14]. Therefore, therapeutic implications of TEE findings may be not established [15]. In stroke patients with PFO, ASA or other minor CSE, cardioembolism is conceivable in the absence of other defined causes of stroke and in the presence of congruous clinical and imaging data. Actually, in stroke patients with isolated PFO, its direct involvement in the cerebral accident is supported by the concomitance of several situations favouring paradoxical embolism (deep venous thrombosis or thrombophilic conditions and stroke onset during Valsalva-like manoeuvres).

Few authors have investigated the occurrence of minor CSE in the various stroke subtypes [16, 17] as well as the relationship between neuroimaging patterns and TEE findings in patients in which major arterial and CSE have been ruled out [18].

The present study aimed to analyse (1) the prevalence of PFO, ASA and other minor CSE by means of TEE in ICVD patients without arterial and major CSE compared to a control population and (2) the relationship between the detection of minor CSE and the topography of stroke at neuroimaging.

Methods

Case Patients

We analysed the records of consecutive patients referred to our neurologic ward between January 1994 and February 2000 with a diagnosis of stroke or transient ischaemic attack (TIA) who underwent TEE. Stroke was defined as an acute ischaemic neurologic deficit which persisted at least 24 h. TIA was diagnosed when the deficit resolved within 24 h. We excluded patients whether (1) high-risk embolic cardiac abnormalities (atrial fibrillation, sick sinus syndrome, prosthetic aortic or mitral valve, endocarditis, rheumatic mitral stenosis, recent myocardial infarction, dilated cardiomyopathy, or previously documented intracardiac thrombus, tumour, or left ventricular aneurysm) were evident at clinical or instrumental examination; (2) atheromatous stenosis (>50%) of vertebral or internal carotid arteries ipsilateral to the ischaemic area, was assessed by extracranial duplex ultrasonography (EDUS), angio-MRI or conventional angiography; (3) other pathologic conditions (i.e. arterial dissection, vasculitis, etc.) were identified as stroke mechanism; (4) TIA symptoms were discordant to ischaemic areas on CT/MRI. We included 175 patients (88 males and 87 females; mean (SD) age, 49.7 (12) years) who were listed in our stroke data bank.

Diagnostic Evaluation and Assessment of Risk Factors

Besides physical examination and routine laboratory studies – including complete lipid and coagulation profiles (antiphosholipid antibodies, antithrombin III, protein C and S free plasma levels and, in the last 2 years, activated protein C resistance and prothrombin polymorphism detection) – all patients underwent cranial CT at admission, ECG, EDUS, transthoracic echocardiography (TTE) and TEE. Whenever necessary, a second cranial CT (80%), brain MRI (60%), conventional angiography (30%) or angio-MRI (25%) was obtained. A venous ultrasonography assessment of lower limbs was performed in 60% of PFO patients. Traditional vascular risk factors were defined according to current accepted criteria [19].

Clinical and Imaging Stroke Classification

Patients were divided in two groups: the lacunar (LAC) and the nonlacunar group (N-LAC). Patients were included in the LAC group in the presence of classical lacunar syndrome and (1) normal imaging findings or (2) subcortical lesion with a diameter <1.5 cm, located in the typical territory supplied by deep or superficial small perforating arteries (basal ganglia, thalamus and brainstem) without the morphologic and topographic distribution consistent with partial internal border zone infarcts [20].

The N-LAC group included patients with cerebral or cerebellar cortical (territorial) infarcts, presumably due to an embolic occlusion of a major pial artery or its division branch. Patients with subcortical ischaemic lesion were assigned to the N-LAC group if (1) the lesion was >1.5 cm in diameter (as in striatocapsular infarction) [21] or if (2) the clinical picture at the onset differed from a lacunar syndrome or suggested a larger ischaemic lesion indicative of an embolic mechanism (as thalamic lacunae in patients with a 'top of the basilar artery' syndrome at onset) [22]. Classification was performed independently by two neurologists blinded to the TTE and TEE data.

By using these criteria, 106/175 (60.6%) patients were assigned to the N-LAC group and 69/175 (39.4%) to the LAC one. In 10/69 (14.5%) LAC patients, ischaemic lesions were only evident on MRI. One patient had a pure motor lacunar syndrome with normal neuroimaging data. The topography of ischaemic lesions was the following: (a) in the LAC group, 27/69 patients had a single deep lacuna; 22/69 multiple deep lacunae; 10/69 a single thalamic lacunae; 10/69 a brainstem lacuna, and (b) in the N-LAC group, 51/106 patients had a superficial middle cerebral artery infarction; 18/106 a posterior cerebral artery infarction; 4/106 an anterior cerebral artery infarction; 21/106 an isolated cerebellar infarction; 8/106 a striatocapsular infarction; 4/106 isolated thalamic lacunae in patients with a 'top of the basilar artery' syndrome.

Control Group

The control group consisted of 78 consecutive patients (40 males and 38 females; mean (SD) age, 53 (12) years) referred to the echocardiography laboratory for TEE during the same period as case patients for indications other than a search for a cardiac source of embolism. These patients had no history of ICVD or heart disorders. TEE was achieved because of fever of unknown origin in 20 subjects, suspected aortic dissection in 20 subjects, neurological conditions other than ICVD in 18 subjects, and exclusion of PFO in 20 healthy subjects who wanted to be enrolled in a scuba diving activity.

Echocardiographic Studies

TTE and TEE were performed within 2 weeks from the onset of symptoms. M-mode and two-dimensional (2D) TTE were obtained by placing the patient in the lateral position using a Hewlett-Packard Sonos 2000 ultrasonograph with a 2.5-MHz transducer. Colour TEE was performed with a omniplane 5-MHz transoesophageal transducer linked to a Hewlett-Packard Sonos 2000 Imaging System (Hewlett-Packard Co., Andover, Mass., USA). TEE examinations were performed exclusively for diagnostic purposes after informed consent was obtained from patients (or relatives). In each patient a detailed evaluation of the fossa ovalis region was achieved with the atrial septum perpendicular to the ultrasound beam. Magnification was selected to fill the imaging sector with both atria separated by the interatrial septum. Special attention was given to morphologic alterations, such as defects in the continuity of the atrial septum, double contour (on horizontal view) or flap-like valvular appearance of the upper rim of the foramen ovale (on vertical view), abnormal bulging, tumour masses. Echocardiographic contrast studies were performed with 8 ml of saline solution and 2 ml of blood mixed by means two syringes connected by a three-way stopcock and injected rapidly into an antecubital vein. Contrast injection was administered during normal respiration and, when possible, was repeated during Valsalva's manoeuvre to increase sensitivity. TEE examinations were recorded continuously on S-VHS videotape for subsequent analysis. Video recordings of each patient were reviewed independently by two cardiologists trained in echocardiography in a frame-to-frame analysis.

For diagnosis of a PFO, the following criteria were considered: (1) no evidence of continuity defect of atrial septum on 2D TTE; (2) at least one microbubble crossing the atrial septum and appearing in the left atrium within three heart cycles after opacification of the right atrium on contrast TEE, without evidence of a negative contrast phenomenon in the right atrium adjacent to the atrial septum; (3) a turbulent colour jet within the atrial septum, with a right-to-left shunt and a left-to-right shunt on colour Doppler TTE. Positive contrast studies were semiquantitatively graded according to Stone et al. [23]. Patients were divided in two groups: group 1 consisted of patients with a maximal number of microbubbles in the left atrium of >20 ('large degree of shunt') and group 2 consisted of patients with a maximal number of microbubbles of ≤20 ('small degree of shunt').

ASA was defined according to Hanley et al [24]: (1) a diameter of the base of the aneurysmatic portion of interatrial septum >15 mm; (2) a protrusion of the interatrial septum (or part of it) >15 mm beyond its plane, and (3) a >15 mm phasic excursion of the interatrial septum during the cardiorespiratory cycle.

MP was diagnosed when the four-chamber view showed protrusion into the left atrium of >3 mm beyond the valve plane by one or both leaflets. Redundancy of the mitral leaflets was assessed by measuring the thickness of the mitral-valve echoes during diastole. Therefore, we considered a 'redundant' MP when either leaflet had a thickness of 5 mm or more and a 'nonredundant MP' when a leaflet's thickness was <5 mm. MMD was defined in the presence of a mitral valve redundancy without prolapse.

AA were diagnosed in the presence of an evident thickness of aortic wall in the ascending tract or proximal arch [2]. They were defined simple atheromas when plaques were <3.9 mm and complicated atheromas when plaques were >4 mm thick or with an irregular surface suggestive of ulceration or with highly mobile elements (irrespective to thickness).

Statistical Analysis

A Statview program was used for statistical analysis. Analysis of differences between ICVD patients and controls and between LAC and N-LAC subtypes were performed using χ^2 test with the Yates' correction for categorical variables (sex, diabetes, hypertension, smoking, PFO, ASI, degree of shunt) and Student's t test for independent sample for continuous variable (age). A level of $p < 0.05$ was considered to be statistically significant.

The significant variables in the univariate analysis were then included in a logistic regression model to determine their value as independent risk factors for ICVD versus controls and for N-LAC subtype versus LAC subtype. All variables were dichotomized to obviate linearity assumption. Adjusted odds ratios (ORs), as measures of associations, were used in reporting the results.

Results

General Features

Baseline characteristics and vascular risk factors are detailed in table 1 (ICVD patients vs. controls) and in table 2 (N-LAC vs. LAC). Mean age was similar among ICVD patients and controls. The percentage of patients younger than 40 years was higher in the N-LAC group than in the LAC one (28.3 vs. 7.2%; p = 0.0005). No difference in sex distribution was found between the overall ICVD population and the control one (table 1) whereas the proportion of males was higher in the LAC versus the N-LAC group (63.7 vs. 41.7%; p = 0.005) (table 2). There was a trend towards a higher prevalence of hypertension in ICVD patients than in controls (40.6 vs. 30.7%; p = 0.08) and towards a lower percentage of smokers (26 vs. 35.9%; p = 0.08) (table 1). Regarding stroke subtype, hypertension and diabetes were significantly more frequent in the LAC group (58 and 13%) than in the N-LAC one (29.2 and 3.8%). The frequency of smoking was similar between the two ICVD subtypes (table 2). General features with respect to age classes are shown in table 3 and 4 (ICVD vs. controls) and table 5 and 6 (N-LAC vs. LAC).

TEE Findings

TEE findings are detailed in table 7 (ICVD patients vs. controls) and in table 8 (N-LAC vs. LAC).

Table 1. Baseline characteristics and vascular risk factors in ICVD patients (N-LAC and LAC) and controls; differences between groups (t test or χ^2 test)

	ICVD patients		Controls		Differences
	n	%	n	%	
Cases	175	100	78	100	
Age (mean), years	49.7		53.2		NS
<40 years	35	20	8	10.2	NS (p = 0.06)
<50 years	83	47.4	30	38.5	NS
<60 years	143	81.7	60	76.9	NS
Males	88	50.3	40	51.3	NS
Diabetes	13	7.4	6	7.6	NS
Hypertension	71	40.6	24	30.7	NS (p = 0.08)
Smoker	46	26	28	35.9	NS (p = 0.08)
Stroke	136	77.7			
RIND	24	13.7			
TIA	15	8.5			

RIND = Reversible ischemic neurologic deficit.

Table 2. Baseline characteristics and vascular risk factors in N-LAC and LAC subtypes; differences between groups (t test or χ^2 test)

	N-LAC		LAC		Differences
	n	%	n	%	
Cases	106	60.6	69	39.4	
Age (mean), years	50.2		48.1		NS
<40 years	30	28.3	5	7.2	p = 0.0005
<50 years	53	50	26	37.7	NS
<60 years	88	83	55	79.7	NS
Males	44	41.7	44	63.7	p = 0.005
Hypertension	31	29.2	40	58	p = 0.0003
Diabetes	4	3.8	9	13	p = 0.03
Smoker	27	25	19	27.5	NS
Stroke	80	75.5	56	81.2	
RIND	13	12.3	11	15.9	
TIA	12	11.3	3	4.3	

Table 3. Vascular risk factors and TEE findings in ICVD patients (N-LAC and LAC) and controls aged ≤50 years; differences between groups χ^2 test)

	ICVD age ≤50 years		Controls age ≤50 years		p value
	n	%	n	%	
Cases	79	100	27	100	
Males	37	46.8	16	59.2	NS
Diabetes	1	1.2	2	7.4	NS
Hypertension	24	30.3	2	7.4	p = 0.01
Smoker	22	27.8	12	44.4	NS
PFO	33	41.7	6	22.2	p = 0.05
ASA	9	11.3	0	0	NS
MP	3	3.8	0	0	NS
AA	1	1.2	1	3.7	NS

Table 4. Vascular risk factors and TEE findings in ICVD patients (N-LAC and LAC) and controls aged >50 years; differences between groups χ^2 test)

	ICVD age >50 years		Controls age >50 years		p value
	n	%	n	%	
Cases	96	100	51	100	
Males	51	53.1	24	47.0	NS
Diabetes	12	12.5	4	7.8	NS
Hypertension	47	48.9	22	43.1	NS
Smoker	24	25.0	16	31.3	NS
PFO	22	22.9	7	13.7	p = 0.05
ASA	12	12.5	1	1.9	p = 0.07
MP	3	3.1	1	1.9	NS
AA	20	20.8	7	13.7	NS

Table 5. Vascular risk factors and TEE findings in N-LAC and LAC stroke subtypes, aged ≤50 years; differences between groups (χ^2 test)

	N-LAC age ≤50 years		LAC age ≤50 years		p value
	n	%	n	%	
Cases	53	100	26	100	
Males	21	39.6	16	61.5	p = 0.02
Diabetes	0	0	1	3.8	NS
Hypertension	11	20.7	13	50.0	p = 0.003
Smoker	15	28.3	7	26.9	NS
PFO	27	50.9	6	23.0	p = 0.03
ASA	8	15.0	1	3.8	NS (p = 0.07)
MP	3	5.6	0	0	NS
AA	1	1.8	0	0	NS

Table 6. Vascular risk factors and TEE findings in N-LAC and LAC stroke subtypes aged >50 years; differences between groups (χ^2 test)

	N-LAC age >50 years		LAC age >50 years		p value
	n	%	n	%	
Cases	53	100	43	100	
Males	23	43.3	28	65.1	p = 0.03
Diabetes	4	7.5	8	18.6	NS
Hypertension	20	37.7	27	62.7	p = 0.04
Smoker	12	22.6	12	27.9	NS
PFO	16	30.1	6	13.9	p = 0.04
ASA	9	16.9	3	6.9	NS
MP	3	5.6	0	0	NS
AA	9	16.9	11	25.5	NS

Table 7. TEE findings in ICVD patients (N-LAC and LAC) and controls; differences between groups (χ^2 test)

	ICVD		Controls		p value
	n	%	n	%	
Cases	175	100	78	100	
PFO	55	31.4	13	16.6	p = 0.02
ASA	21	12.0	1	1.3	p = 0.003
PFO + ASA	13	7.4	0	0	NS
MP	6	3.4	1	1.2	NS
AA	21	12	8	10.2	NS

Table 8. TEE findings in N-LAC and LAC subtypes; differences between groups (χ^2 test)

	N-LAC		LAC		p value
	n	%	n	%	
Cases	106	60.6	69	39.4	
PFO	43	40.6	12	17.4	p = 0.0005
ASA	17	16.0	4	5.8	p = 0.05
PFO + ASA	10	9.4	3	4.3	NS
MP	6	5.7	0	0	NS
AA	10	9.4	11	15.9	NS

Table 9. Predictors of infarct (ICVD patients: LAC and N-LAC) versus controls (logistic regression)

	OR	95% CI	p value
PFO	3.8	2.7–7.9	0.009
ASA	8.01	3.0–16.1	0.008
Age <40 years	0.96	0.85–1.75	NS
Hypertension	1.23	0.90–2.1	NS
Smoker	0.54	0.41–1.43	NS

Table 10. Predictors of N-LAC subtype (logistic regression)

	OR	95% CI	p value
Males	0.59	0.29–1.17	NS
Age <40 years	0.97	0.94–1.1	NS (p = 0.08)
Hypertension	0.38	0.19–0.77	p = 0.01
Diabetes	0.33	0.12–1.25	NS
Smoker	1.2	0.55–2.05	NS
PFO	2.24	1.24–4.92	p = 0.04
ASA	3.28	0.98–10.91	p = 0.05

PFO rate was higher in overall ICVD patients than in controls (31.4 vs. 16.6%; p = 0.02) and in the N-LAC group versus the LAC one (40.6 vs. 17.4%; p = 0.0005). Notably, PFO frequencies in LAC patients and in controls were similar. In the overall ICVD population, as well as in the N-LAC and LAC subtypes, PFO rate was higher in patients aged <50 years (table 3–6). In addition, we found a higher frequency of PFO in younger patients (aged <50 years) with respect to older ones (aged >50 years) in N-LAC (p = 0.03) but not in the LAC subtype.

Table 11. Predictors of infarct (LAC and non-LAC) versus controls (logistic regression)

	Age ≤50 years			Age >50 years		
	OR	95% CI	p value	OR	95% CI	p value
Hypertension	1.9	0.96–3.1	NS	1.52	0.74–3.11	NS
Smoker	0.53	0.19–1.45	NS	1.58	0.70–2.4	NS
PFO	4.58	2.36–8.5	0.008	2.1	1.9 –7.8	0.012
ASA						

Table 12. Predictors of N-LAC type of infarct versus LAC type of infarct (logistic regression)

	Age ≤50 years			Age >50 years		
	OR	95% CI	p value	OR	95% CI	p value
Sex	0.3	0.11–1.08	0.06	0.9	0.37–1.23	0.2
Hypertension	0.26	0.1 –0.82	0.02	0.4	0.17–1.04	0.06
Diabetes	0.31	0.1 –1.4	0.17	0.30	0.08–1.49	0.16
PFO	2.6	1.49–5.49	0.03	2.2	1.05–4.88	0.05
ASA	2.7	1.4 –15	0.03	2.9	0.91–9.1	0.06

ASA rate was significantly higher in overall ICVD patients than in controls (12 vs. 1.3%; p = 0.003) (table 7) and in the N-LAC group compared to the LAC one (16 vs. 5.8%; p = 0.05) (table 8). There were no significant differences in ASA frequency in the two groups of age (table 3, 4). Besides, ASA was associated with PFO in 13/21 of ICVD subjects (10/17 N-LAC and 3/4 LAC patients).

MP was detected in 6 (3.4%) ICVD subjects (all in the N-LAC group) and in 1 (1.2%) of the control subjects; in 5/6 N-LAC subjects and in the control case a redundant myxomatous MP was evident (table 8). Because of the small number of cases, no statistical inference could be drawn.

AA was detected in 21/175 case patients and in 8/78 controls (12 vs. 10.2%; NS). Among ICVD patients, its frequency was lower in the N-LAC group than in the LAC one (10/106 (9.4%) vs. 11/69 (15.9%); NS). No complicated AA was detected. Except in 1 subject, AA were always detected in patients aged >50 years.

On multivariate analysis, PFO and ASA were independently associated with overall ICVD events (respectively OR = 3.8 with 95% CI = 2.7–7.9 and OR = 8.01 with 95% CI = 3.0–16.1) (table 9). Moreover, just PFO was an independent predictor of the N-LAC subtype versus the LAC one (OR = 2.24, 95% CI = 1.24–4.92) (table 10). As expected, hypertension was negatively associated with the N-LAC subtype (OR = 0.38; 95% CI 0.19–0.77). The associations of PFO with all ICVD events and with N-LAC subtype were stronger in patients aged <50 years than in overall population and subjects aged >50 years (respectively OR = 4.58; 95% CI = 2.36–8.5 and OR = 2.6; 95% CI = 1.49–5.49). Notably, in younger patients, ASA was independently associated with the N-LAC subtype (table 11, 12).

Severity of PFO

A large degree of shunt associated with PFO (see Methods) occurred in 45.5% of ICVD cases versus 23.1% of controls (NS) (table 13) and in 53.5% of N-LAC patients versus 16.7% LAC ones (p = 0.05) (table 14). Among the stroke population a large PFO was peculiar of N-LAC subtype: indeed, 92% (23/25) of patients with a large shunt were N-LAC cases versus 66.6% (20/30) with a small shunt (p = 0.05) (table 15). PFO was associated with ASA in 13/55 (23.6%) of ICVD patients but in none of controls (table 13) without significant difference in the N-LAC and LAC subtypes (table 8). Thrombotic stratifications on septal anomalies were never detected.

Risk Factors for Paradoxical Embolism

Deep vein thrombosis was reported in just 2/55 (3.7%) patients with PFO, but a lower limb ultrasonography was achieved only in 60% of cases and a retrograde venography in none of them (table 16). Four N-LAC patients with PFO had an inherited coagulopathy (APC resistance in 2, protein S deficiency and prothrombin polymorphism in

Table 13. Severity of PFO regarding the degree of shunt and the concomitance of ASA; differences between ICVD patients (N-LAC and LAC) and controls (χ^2 test)

	ICVD patients (N-LAC + LAC)		Controls		Differences
	n	%	n	%	
Cases	55	100	13	100	
Small shunt	30	54.5	10	76.9	NS
Large shunt	25	45.5	3	23.1	NS
Isolated PFO	42	77	13	100	NS
PFO + ASA	13	23.6	0	0	NS

Table 14. Severity of PFO regarding the degree of shunt and the concomitance of ASA; differences between N-LAC and LAC subtypes (χ^2 test)

	N-LAC		LAC		Differences
	n	%	n	%	
Cases	43	100	12	100	
Small shunt	20	46.5	10	83.3	p = 0.05
Large shunt	23	53.5	2	16.7	p = 0.03
Isolated PFO	33	77	9	75	NS
PFO + ASA	10	23.2	3	25	NS

Table 15. Distribution of large and small PFO in N-LAC and LAC subtypes

Type of infarct	Large PFO		Small PFO		Differences (χ^2 test)
	n	%	n	%	
Cases	25	100	30	100	
N-LAC	23	92	20	66.6	p = 0.05
LAC	2	8	10	33.3	

Table 16. Risk factors for paradoxical embolism in patients with PFO

	ICVD patients (N-LAC + LAC)		N-LAC		LAC	
	n	%	n	%	n	%
Cases	55	100	43	100	12	100
TVP[1]	2	3.7	2	4.6	0	0
Coagulopathies[2]	4	7.2	4	9.3	0	0
Onset[3]	14	25.5	12	27.9	2	16.6

[1] Only 60% underwent lower limb ultrasonography.
[2] ATIII, proteins C and S were detected in all patients; APC resistance in 80%; prothrombin mutation in 50% of patients.
[3] Onset concomitant to increased intrathoracic pressure: physical activity or Valsalva-like manoeuvres (squatting, sexual activity, defecation, cough).

1), nevertheless without signs or symptoms of deep venous thrombosis. Onset during physical activity or Valsalva-like manoeuvres (squatting, sexual activity, defecation, cough) was reported in 25.5% stroke patients with PFO, in particular in 27.9% (12/43) of N-LAC patients and in 16.6 % (2/12) of LAC ones. None of ICVD patients had a history of pulmonary embolism.

Discussion

Major CSE are reported to occur more frequently in nonlacunar strokes than in lacunar ones [25] but few data are available regarding the prevalence of minor CSE with respect to stroke subtypes [16, 17]. Atrial septal abnormalities – i.e. PFO and ASA – are frequently detected in patients with juvenile stroke and are not uncommon in general population [14]. Therefore, their role in stroke mechanism may be supported by the concomitance of neuroimaging findings congruous with embolic infarcts, such as nonlacunar 'territorial' infarcts, and of conditions predisposing to paradoxical embolism. Even if TEE seems to be more helpful and 'cost-effective' than TTE in diagnostic evaluation of stroke (particularly to detect minor CSE in patients without evidence of heart diseases) [26–29], its actual role with respect to stroke subtype is not defined.

The aim of our study was to investigate the occurrence of minor CSE in ICVD patients compared to a control population and in two ICVD subtypes defined by the topography of the ischaemic lesion (lacunar and nonlacunar; see Methods) at neuroimaging. The study population was selected from consecutive stroke patients without arterial and major CSE who underwent TEE. Control subjects were patients without stroke or TIA, in which TEE was achieved to investigate cardiopathies different from a CSE.

Patent Foramen ovale

In the present study the prevalence of patients with PFO was significantly higher in the overall ICVD group (31.4%) compared to controls (16.6%) and was similar to previous studies [14]. PFO frequency was significantly higher in N-LAC patients than in LAC ones (40.6 vs. 17.4%); interestingly, LAC patients presented a PFO rate similar to the control population. This evidence does support a nonembolic mechanism in lacunar stroke [25]. In the literature, PFO rate is 10–44% in overall ICVD patients, 31–77% in cryptogenic stroke, 4–25% in stroke due to determined cause, and 3–22% in healthy controls [14]. Such a variability is related to the heterogeneity of the study population, diagnostic tests and inclusion criteria. Few studies distinguished patients with lacunar infarction [16, 17], ruling out or including them in the cryptogenic group. Previous studies [30–32] and a recent meta-analysis [14] reported a significant association of PFO and ASA with ischaemic stroke only in patients <55 years; we also found a higher prevalence of PFO in patients aged <50 years. Besides, in this group of patients, PFO represented a stronger predictor of ischaemic events in the overall ICVD population and in N-LAC subtypes.

The higher rate of 'large' shunts in N-LAC patients versus LAC ones (53.5 vs. 16.7%) is in agreement with the report by Stone et al. [23] and supports the current opinion that shunt entity is a relevant factor in predisposing to cerebral ischaemic events in patients with PFO [29, 33–36]. Besides, the significantly higher rate of N-LAC infarcts versus LAC ones in patients with 'large' PFO (92 vs. 8%) further supports an embolic mechanism in N-LAC patients with PFO.

In the present series, PFO was complicated by an ASA in about 1 out of 5 ICVD patients, without differences between N-LAC and LAC groups, and in none of controls. This seems to confirm the importance of ASA as risk factor for stroke in PFO patients [37] even if a definite conclusion could not be drawn in our study because of the small number of patients in the control group. Regarding clinical and instrumental findings of paradoxical embolism, prevalence of deep vein thrombosis in our PFO patients is lower than in other studies [38, 39]; this may be due to the limited number of patients (60%) that achieved a compression ultrasonography (although its diagnostic value is limited in asymptomatic subjects) [40, 41]. Anyway, in some patients with N-LAC stroke and PFO the presence of an inherited coagulopathy may support a mechanism of paradoxical embolism even in the absence of clinical and instrumental signs of venous thromboembolism [42]. That mechanism may also be supported by an abrupt onset during physical activity or Valsalva-like manoeuvre (27.9% in our cases).

Atrial Septal Aneurysm

We observed a significant difference between overall ICVD patients and controls but not between N-LAC and LAC subtypes. ASA frequency in our ICVD series (12%) was similar to that reported in a recent meta-analysis [14] whereas the low rate we observed in controls (1.3%) is in agreement with a recent case-control study [43] and a large autopsy series [44]. Detection rates for ASA ranged from 2 to 17% for stroke, 4 to 25% for cryptogenic stroke, 0.2 to 22% for known stroke cause, and 0 to 15% for controls [14]. Albers et al. [17] reported no difference in PFO rate among all stroke subtypes and a higher prevalence of ASA in LAC groups. Mast et al. [16] observed a low prevalence of PFO and ASA (6.3 and 14.3%) in N-LAC cases (named 'pial artery infarcts') probably because of the inclusion of subjects with other (arterial or cardiac) embolic sources. Several mechanisms have been advocated to explain cerebral ischaemic events in ASA patients: paradoxical embolism (whether a PFO is concomitant) [45], thrombus formation on the septal aneurysm [46], an associated MP [47], and occurrence of supraventricular arrhythmias [48]. In our series, only paradoxical embolism may be suggested: indeed, 61.9% of ASA patients had a right-left shunt but no difference was observed between the two ICVD subtypes.

Differently from PFO, there were no significant differences in ASA frequency in the two groups of age and even a slight prevalence in older patients; however, the interpretation of such findings has to be cautious because of the low number of patients.

Other Sources of Embolism

In the present series the frequency of MP is lower than in some studies [49] but similar to others [50, 51]. This may be related to the strict criteria adopted and is in agreement with the low embolic risk outlined in two recent community-based studies [52, 53]. The high proportion of redundant MP suggests that the myxomatous valve stratification rather than the prolapse itself is determinant for embolic events [51]. However, the low number of patients in our study does not allow any statistical inference.

We found no difference in the frequency of AA between ICVD patients and controls as well as between N-LAC and LAC subtypes. Transoesophageal [2, 54, 55] and autoptic studies [56] reported a higher frequency of AA in patients with cryptogenic stroke being only large protrud-

ing (>4 mm) and complicated AA risk factors for stroke or recurrent brain infarction [2, 54]. The correlation from AA and stroke is reported for patients aged >60 years independently from the presence of carotid stenosis, atrial fibrillation [2, 54, 55] and peripheral artery disease [54]. In our study the low frequency of AA and the absence of complicated AA may be due to the young age of the patients (only 18.3% being >60 years) as well as to the exclusion of patients with significant carotid stenosis and myocardial infarction (strongly associated with generalized atheromatosis). As expected, the great majority of AA was found in older patients, only 1 ICVD patient with AA being <50 years.

Conclusions

The present study confirms TEE as an important diagnostic tool in stroke patients when arterial and major CSE are ruled out. Its utility differs on the basis of etiopathogenesis and topography of ischaemic lesions, being more relevant in patients with nonlacunar infarctions. So, definition of stroke subtype is critical to the echocardiographic assessment of ICVD patients and the decision to perform a TEE study in patients with stroke or TIA should be based on the likelihood of an embolic mechanism according to clinical and neuroimaging data. PFO and ASA are the most frequent minor CSE detected in stroke patients. Even if clinical and instrumental findings congruous with venous thromboembolism were rarely detected, some features strongly support its role in the pathogenesis of cerebral accidents: on the one hand the higher prevalence of PFO as well as 'large' PFO in N-LAC patients and, on the other one, the not uncommon onset during Valsalva-like manoeuvres and the presence of thrombophilic conditions. In patients with lacunar infarction, the low occurrence of cardiopathies and the high rate of hypertension and diabetes suggest first that the underlying mechanism is a primary vessel disease rather than an embolic occlusion and second that the detection of CSE may represent an incidental finding. In patients with MP, stroke risk seems to be associated with the myxomatous valve thickness rather than with the prolapse itself. Finally, our data highlights that searching aortic atheromas in not-elderly stroke patients without significant extracranial vessel atheromatosis appears poorly useful.

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